

Ninth Quarterly Progress Report
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**The Neurophysiological Effects of
Simulated Auditory Prosthesis
Stimulation**

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1 Introduction

The purpose of this contract work is to explore issues involving the transfer of information from implantable auditory prostheses to the central nervous system. Our investigation is being pursued along multiple tracks and includes the use of animal experiments and computer model simulations to:

1. Characterize the fundamental spatial and temporal properties of intracochlear stimulation of the auditory nerve.
2. Evaluate the use of novel stimuli and electrode arrays.
3. Evaluate proposed enhancements in animal models of partial degeneration of the auditory nerve.

In this ninth quarterly progress report (QPR), we focus on the first of these three aims, reporting on experimental results that shed light on differences in neural excitation processes that occur with monopolar and bipolar intracochlear stimulation of the auditory nerve. Our goal of this research was to identify neurophysiological mechanisms that may be related to clinical reports of perceptual differences between these two modes of prosthetic stimulation. Although we have just begun this investigation, the results suggest that firing properties of the auditory nerve form at least part of the basis for reported clinical results.

2 Summary of activities in this quarter

In our ninth quarter (1 October - 31 December, 2001), the following activities related to this contract were completed:

1. In October 2001, we attended the 32nd Neural Prosthesis Workshop in Bethesda and presented a summary of progress on the research under this contract.
2. A manuscript detailing comparisons of computational algorithms for simulating fibers with stochastic sodium channels has been accepted by the *Annals of Biomedical Engineering*.
3. Changes to our network infrastructure resulted in the loss of access to our Macintosh cluster for complex simulations for the past year. Software upgrades have been made to regain the use of this system. We have benchmarked it at over 6 GFlops for single-precision calculations.

Using the new VAST FORTRAN and c-compilers and MacMPI, we expect to be able to both automatically vectorize and parallelize our simulation code, permitting computational speed to scale with the number of Macs in our cluster. Each new Mac added should add over 2 GFlops per CPU. We intend to use this new capability to tackle refractory simulations that were too computationally intensive for a single CPU.

4. We began histological assessment of a feline auditory nerve trunk implanted with an experimental 3-shank thin-film electrode. This assessment is part of a histological survey being done to quantify the degree of damage that results from electrode insertion. Results will be reported in a later QPR.
5. We recorded both gross-potential (i.e., ECAP) and single-fiber responses from cats using an intracochlear banded electrode array in order to assess responses under different electrode configurations. Results of that work are presented in this progress report.

3 Effects of electrode configuration on the ensemble response of the nerve

3.1 Introduction

Evoked-potential studies reveal marked differences in fiber recruitment obtained with monopolar and bipolar intracochlear stimulation. These differences are manifest at the inferior colliculus (Merzenich & White, 1977; Black & Clark, 1980), brainstem (Marsh et al., 1981; Hatsushika & Funasaka, 1989; Abbas & Brown, 1991; Miller et al. 1995), and auditory nerve (van den Honert & Stypulkowski, 1987; Hartmann & Klinke, 1990; Brown et al. 1996). Comparisons of monopolar and bipolar psychophysical thresholds in implanted animals (Miller et al. 1995; Pfingst et al. 1995a) and humans (Pfingst et al., 1995b; Pfingst et al., 1997) show trends consistent with the physiological data. The single-fiber work of van den Honert & Stypulkowski (1987) clearly demonstrated that monopolar stimulation produces a broader spatial pattern of excitation than does bipolar stimulation. From these findings, it is sometimes assumed that the more focused stimulation modes of bipolar and tripolar configurations provide advantages over monopolar stimulation. Monopolar excitation has often been considered “too broad”. Also,

the more focused modes could possibly excite the more peripheral neural processes, arguably providing more stochastic spike patterns.

Clinical results, however, have suggested a somewhat more complex picture. It has long been known that monopolar stimulation can provide spatial cues unique to each electrode that are useful for pitch perception (Eddington, 1980). In recent years, cochlear implant users have been shown to often prefer the percept provided by monopolar stimulation or broader bipolar electrode configurations. In some cases, subjects enjoy improved speech perception with this mode (Lehnhardt et al., 1992; von Wallenberg et al., 1995; Zwolan et al., 1996; Pfungst et al., 1997; Kileny et al. 1992). Pfungst et al. (1997) appealed to the model of White (1984) to forward a possible general mechanism for these results: If monopolar stimulation results in generally lower firing rates of individual fibers, those lower rates may confer temporal and spatial response patterns in ways different from bipolar excitation.

The above observations suggest that monopolar stimulation can be advantageous for the encoding of electric stimuli. We hypothesized that the stochastic properties of auditory nerve responses - namely probabilistic firing and jitter - are more pronounced for monopolar excitation than for bipolar excitation. Our goal was to examine the degree to which these effects are observed at both the single-fiber level and the ensemble (whole-nerve) level using pulsatile stimuli similar to those used in modern implants. We also sought to analyze published single-fiber data as another means of addressing this hypothesis.

3.2 Methods

Three adult cats with normal hearing were used in acute experimental sessions, deafened with kanamycin and ethacrynic acid (Xu et al., 1993) prior to data collection. A Nucleus-type electrode array (scaled for use in the cat cochlea) with 8 banded contacts was inserted into the round window. Stimuli were in the form of 40 microsecond per phase monophasic or biphasic rectangular current pulses delivered at a rate of 33 pps. Responses to both stimulus polarities were recorded separately. Both single-fiber and electrically evoked compound action potential (ECAP) measures were obtained using a posterior-fossa approach to the nerve.

Stimuli were delivered through 3 electrode configurations: monopolar, bipolar, and tripolar. The second most apical electrode (electrode 2) was

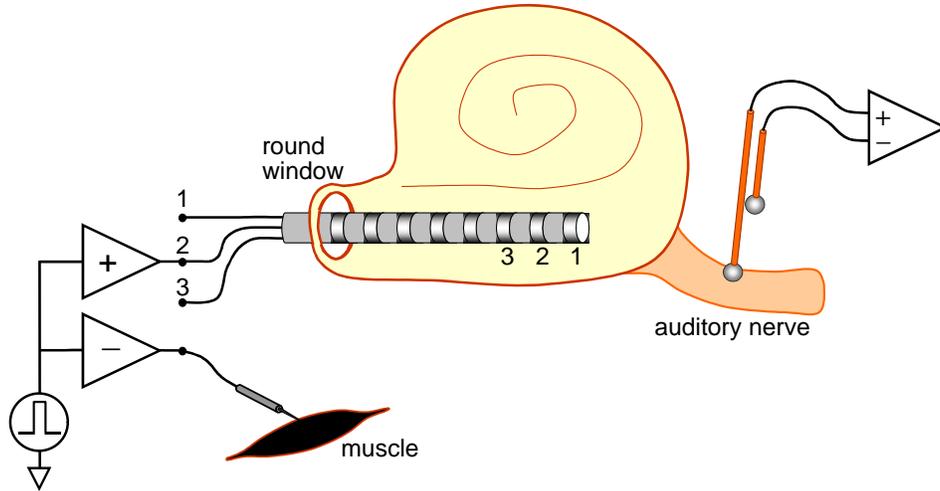


Figure 1: Schematic illustration of stimulation configurations used in the experiments of this study. The figure depicts monopolar stimulation through the second most apical electrode and gross-potential electrodes positioned near the surgically exposed auditory nerve.

chosen as the reference electrode and was used in all three configurations. Figure 1 depicts monopolar stimulation through electrode 2 and an extra-cochlear ground electrode. Single-fiber input-output functions were obtained using our standard techniques (Miller et al., 1999a) which typically involved obtaining responses to 100 repeated stimulus presentations in order to obtain firing statistics (firing efficiency, mean latency, jitter) and an estimate of relative spread (a measure of dynamic range).

3.3 Results

3.3.1 Example response waveforms

Figure 2 depicts examples of recorded single-fiber (top) and ECAP (bottom) waveforms and definitions of measures used for some of the analyses presented in this report. Both single-fiber and ECAP responses were recorded using surgical exposure of the nerve and placement of electrodes in or on the nerve trunk. As is typical for our single-fiber measures, threshold is defined as the level producing a firing efficiency (FE) of 50%. As we typically do, we quantified ECAP amplitude as the potential difference between the N1 and P2 peaks. ECAP latency was measured from the onset of the stimulus

artifact to the N1 peak. We also characterize the width of the ECAP waveform as its width measured at the half-way point along its amplitude (i.e., the 50% width, as shown in the figure).

3.3.2 ECAP growth and latency

Figure 3 shows examples of how ECAP amplitude and latency vary with stimulus level. Consistent with previous reports, bipolar excitation produces much lower rates of growth. Tripolar stimulation produces even slower growth. An interesting finding here is that, for 2 of the 3 subjects, monopolar latencies are considerably less than those obtained with bipolar stimulation, suggesting that monopolar excitation may occur at relatively central membrane sites. This possible monopolar-bipolar difference in site of excitation could give rise to differing neural responses, as auditory nerve fiber membrane properties are not uniform along their longitudinal dimension.

It is clear from the amplitude plots of Figure 3 that the tripolar electrode configuration recruited relatively few fibers, even at the highest levels tested. It would therefore be difficult to encounter a significant number of single-fiber data and adequately characterize single-fiber responses to tripolar stimulation. Accordingly, we did not pursue that mode of excitation in the single-fiber assessments described below.

3.3.3 Single-fiber measures

As the ECAP is a gross measure of neural activity, it is important to assess the degree to which single-fiber response properties vary with manipulation of electrode configuration. The observation of different monopolar and bipolar ECAP latencies provides additional motivation for conducting the single-fiber comparisons. To that end, single-fiber measures were obtained from 39 fibers from the same three cats using the same electrode configurations and stimuli. Figure 4 presents four graphs which make monopolar/bipolar comparisons of (A) threshold, (B) mean spike latency, (C) spike jitter, and (D) relative spread. Monopolar data are plotted on the abscissa and bipolar data are plotted along the ordinate. Trends are summarized below.

1. Threshold. Of the 39 fibers, 17 failed to respond to the highest levels output to the bipolar configuration. Over all fibers, the mean monopolar threshold was 12 dB lower than the bipolar value. A paired-comparison t-test showed that this difference was highly significant ($p < 0.0001$).

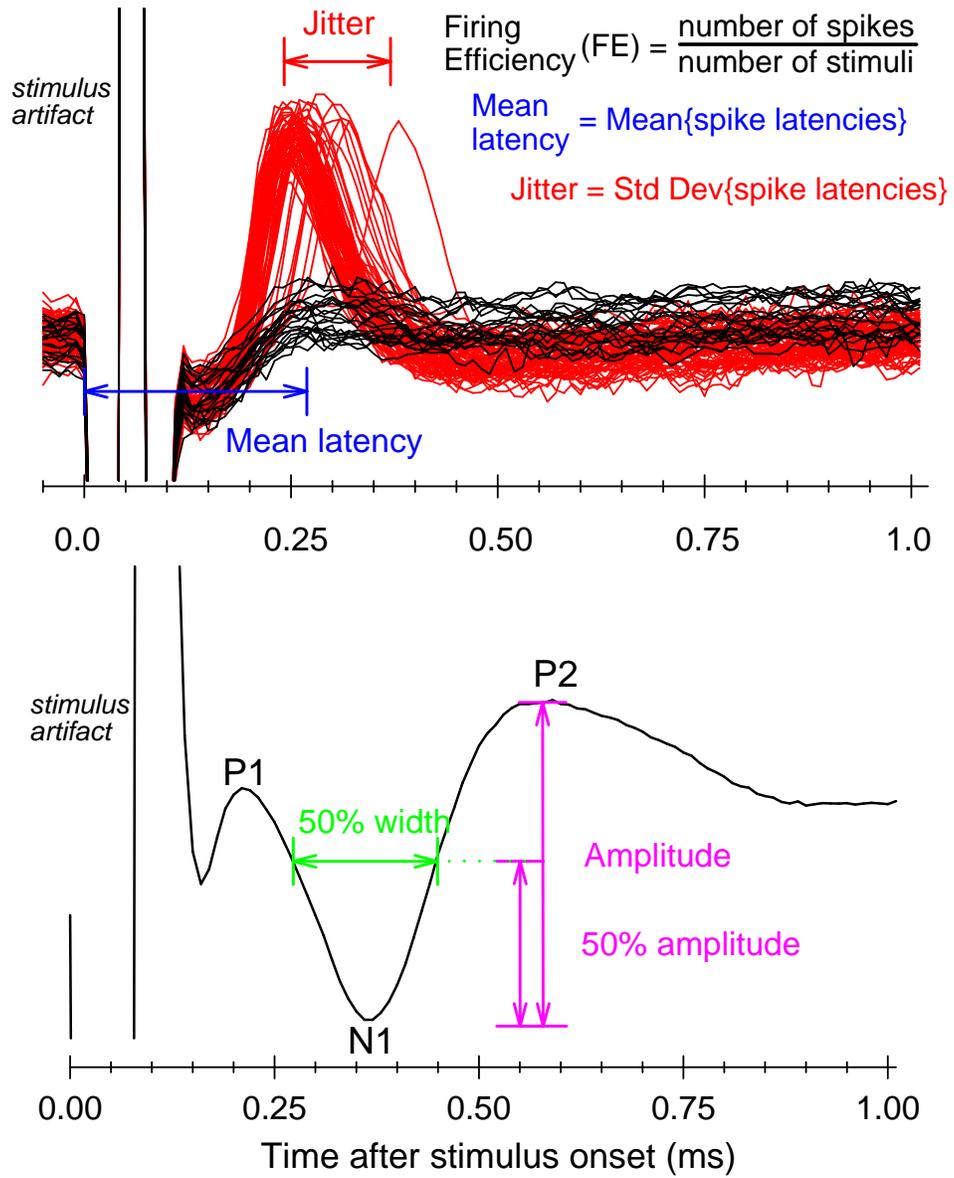


Figure 2: Illustration of the primary single-fiber and ECAP measures used in the analysis presented in this report.

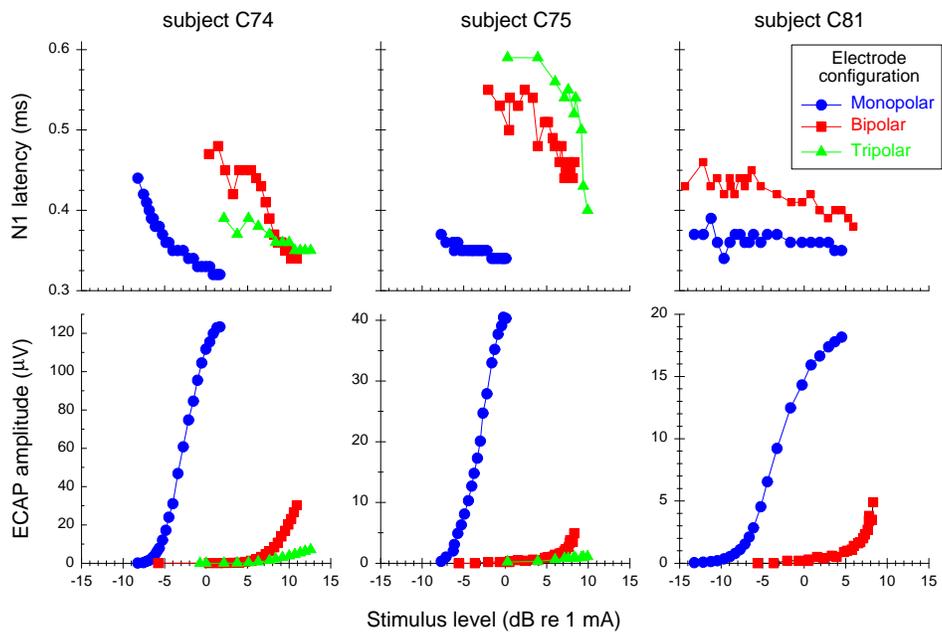


Figure 3: ECAP latency-level (top) and amplitude-level (bottom) functions for different stimulus electrode configurations. Each column presents data from a different subject.

2. Mean latency. Mean latency (measured at 50% firing efficiency) was, on average, about 0.10 ms shorter for bipolar stimulation than for monopolar stimulation. This difference was also statistically significant ($p < 0.0001$).
3. Jitter. Jitter was about the same for both stimulus modes (monopolar: 0.0467 ms; bipolar: 0.0486 ms), as shown by the paired t-test ($p=0.68$).
4. Relative spread. Mean relative spread for monopolar stimulation (0.054) was somewhat greater than the mean bipolar value (0.0325). The t-test result indicated “borderline” statistical significance ($p=0.0532$).

3.3.4 Summary of ECAP and single-fiber trends

Monopolar-bipolar trends in the ECAP data reflected differences observed at the single-fiber level. Specifically, a strong bias toward lower monopolar thresholds and shorter monopolar latencies were observed in both data sets. Interestingly, there was no dependence of single-fiber jitter on electrode configuration. Thus, although sites of excitation may differ across the two stimulus modes, the jitter comparison suggests comparable membrane properties for the two excitation modes. Also, if there is a bias toward greater relative spread for monopolar stimulation, it is a weak trend. As differences in threshold and latency are arguably due to differences in the stimulus fields produced by monopolar and bipolar electrodes, we conclude that intrinsic functional properties of the neural membrane do not vary in a robust way across the two electrode configurations.

Although the membranes excited by monopolar and bipolar stimulation modes exhibit similar functional membrane properties, we believe it is likely that temporal and probabilistic firing properties do vary across the two modes. According to our hypothesis, monopolar excitation results in greater spread of excitation, but lower overall firing probabilities. The trends of Figure 4 are not inconsistent with this notion.

3.3.5 An examination of ECAP morphology

The single-fiber comparisons likely offer only a partial understanding of how the nerve’s response may vary across the two stimulus modes. We therefore refined our hypothesis to account for the likely fact that, for a given level of neural activity, monopolar and bipolar stimulation involve significantly different neural subpopulations. Our monopolar ECAP growth functions

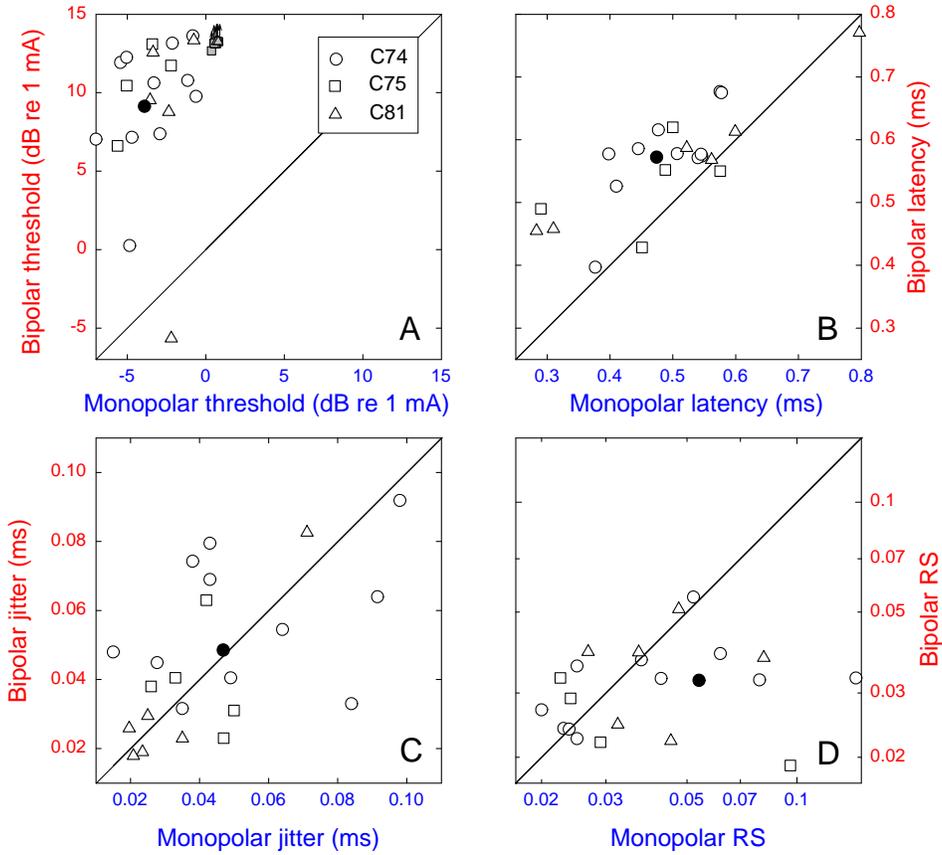


Figure 4: Comparison of single-fiber response properties obtained for bipolar and monopolar stimulation modes. Measures obtained with bipolar stimuli are plotted along the vertical axes while monopolar measures are plotted along the horizontal axes.

were characterized by very steep growth (Figure 3). Given that precipitous growth, we speculated that, over a range of stimulus levels, spike activity arose from a relatively large number of fibers that responded at relatively low firing rates. As the degree of jitter is inversely related to firing efficiency (Miller et al., 1999a), we hypothesized that, in comparison to a comparable level of neural activity, monopolar stimulation produced more ensemble jitter and that greater jitter could be manifested as a widening of the ECAP waveform (relative to the bipolar ECAP).

This notion is reflected in significantly different ECAP waveform morphologies obtained under monopolar and bipolar stimulation. Figure 5 presents ECAP waveforms obtained from one subject with monopolar (top graphs) and bipolar (bottom graphs) stimulation. While the response morphologies varied also with the stimulus polarity, it is evident that monopolar stimulation (in particular, monophasic cathodic stimuli) produced ECAP waveforms that were relatively wide. We also observed such “widening” in a second cat subject from whom such data were collected. We quantified these effects using the 50 percent width measure (i.e., Figure 2). For the responses from the two cats, ECAP widths are plotted as a function of ECAP amplitude in Figure 6. The responses shown were obtained at the lowest stimulus levels at which reliable waveforms could be recorded. In both cases, monopolar stimulation produced wider ECAP potentials at almost all of these low stimulus levels.

3.4 Analysis of published single-fiber data

The most detailed survey of single-fiber monopolar and bipolar thresholds was performed by van den Honert & Stypulkowski (1987). We conducted an analysis of that data to gain additional insight into the hypothesis of this study. The original, graphically presented data were digitized and replotted (Figure 7). Threshold histograms were then created and integrated across current level to produce fiber recruitment curves (Figure 8). Each of the 6 curves shows the proportion of fibers that have reached threshold as a function of stimulus level. Note that the curves of Figure 8 are normalized by the total number of fibers in each data set to facilitate across-condition comparisons. The recruitment curves allow us to estimate, as a function of level, the fraction of fibers that are active, yet not saturated (i.e. $0 < FE < 100\%$). This was done by a piecewise analysis of each curve of Figure 8. We assumed the average fiber has a dynamic range of 2 dB (Miller et al., 1999b). For each curve, we determined, at 1 dB steps of level, the number

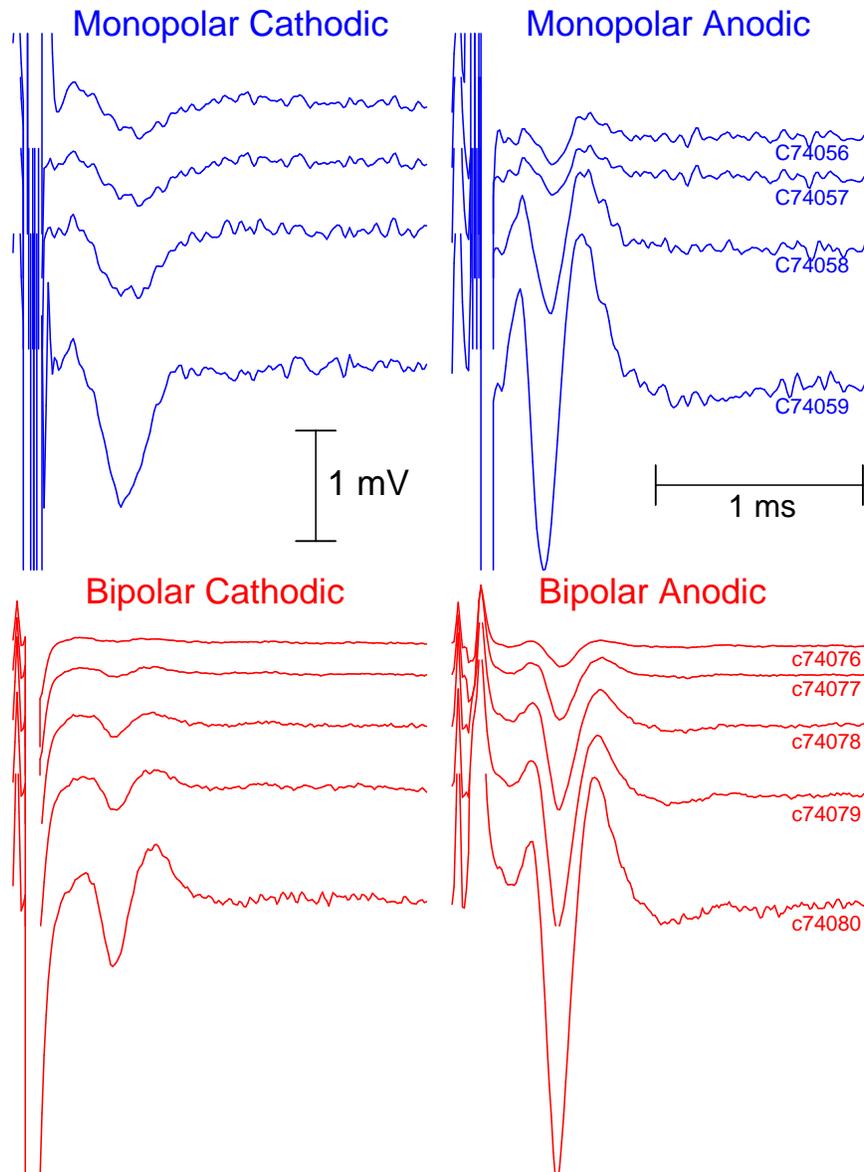


Figure 5: ECAP waveforms obtained from a cat preparation under monopolar (top graphs) and bipolar (bottom graphs) stimulus conditions. Monophasic pulses of cathodic (left column) and anodic (right column) polarity were used. A template-subtraction scheme was used to reduce stimulus artifacts in each response. Uncancelled stimulus artifacts appear over the first 0.2 ms epoch of each waveform.

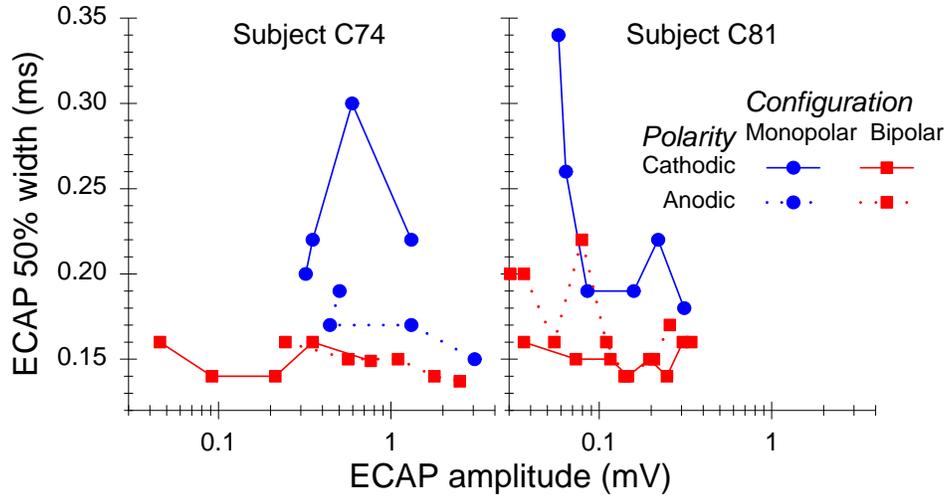


Figure 6: ECAP width as a function of ECAP amplitude for two feline subjects. Stimuli presented by a monopolar electrode produced relatively wide ECAP waveforms.

of fibers within the 2 dB window. These estimates (Figure 9) reveal that, at low stimulus levels, monopolar excitation results in a relatively larger fraction of fibers that respond within their dynamic range. These findings are consistent with our previous analyses and again indicate that monopolar stimulation provides greater ensemble spike jitter. This jitter may be due to a distribution of characteristic latencies across the population (Miller et al., 1999b). We also note that, along with greater jitter, monopolar stimulation also results in a greater number of non-saturated fibers, a condition that could provide for greater transmission of stimulus level information.

3.5 Summary

From the above data analyses, we conclude that monopolar stimulation results in relatively greater ensemble jitter. This greater jitter arises from lower firing efficiencies and a distribution of fiber latencies across the neural population. This greater level of stochasticity may provide a more “naturalistic” pattern of action potential activity that is evident to implant users. Monopolar stimulation also results in a greater number of fibers operating within their dynamic range, providing a means of conveying amplitude information in a more robust way. We note that monopolar-bipolar differences were observed in both our investigation (which employed a Nucleus-type

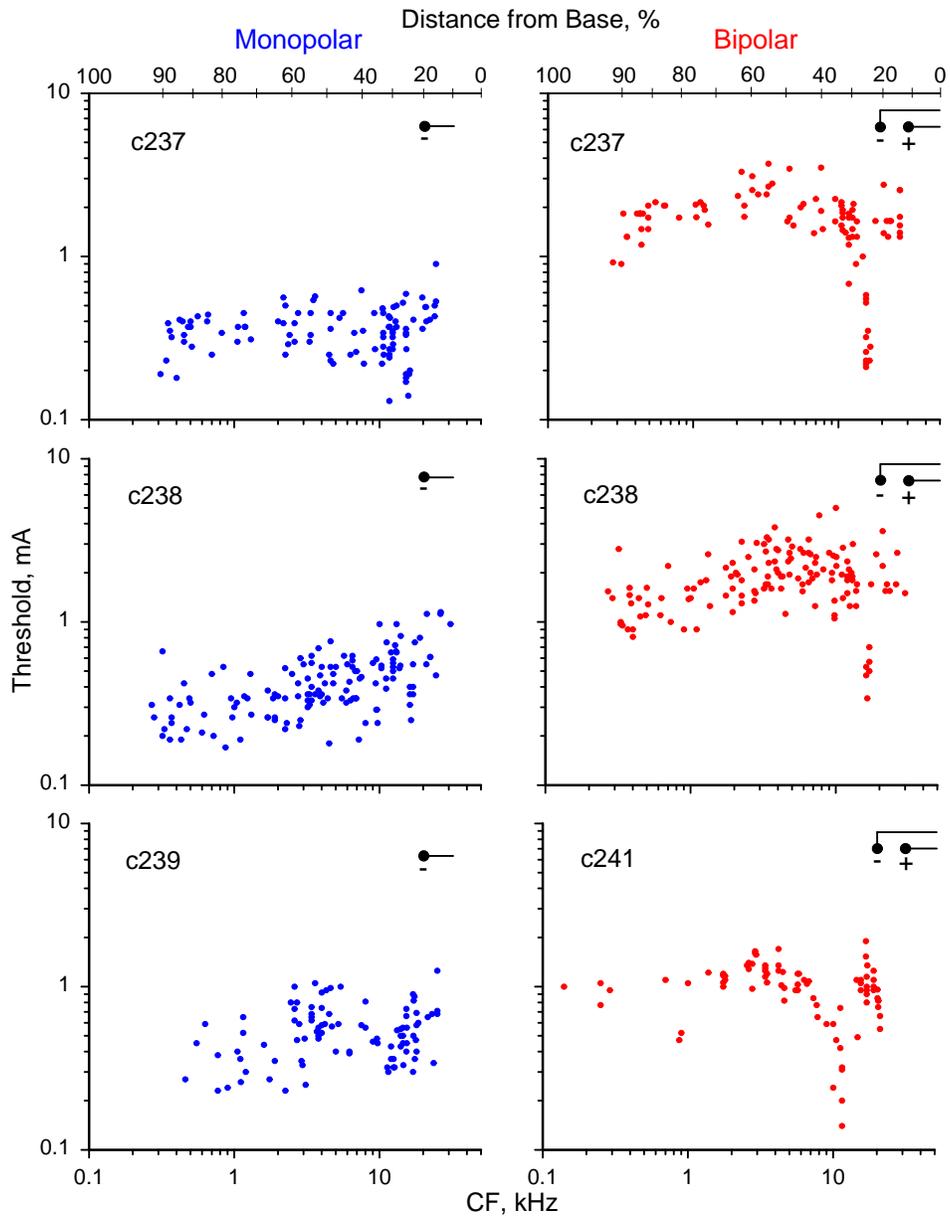


Figure 7: Data from van den Honert & Stypulkowski (1987) showing distribution of auditory nerve fiber thresholds to intracochlear stimulation presented either by an intracochlear monopolar electrode (left column) or an intracochlear bipolar pair (right column). Data were obtained from four cats.

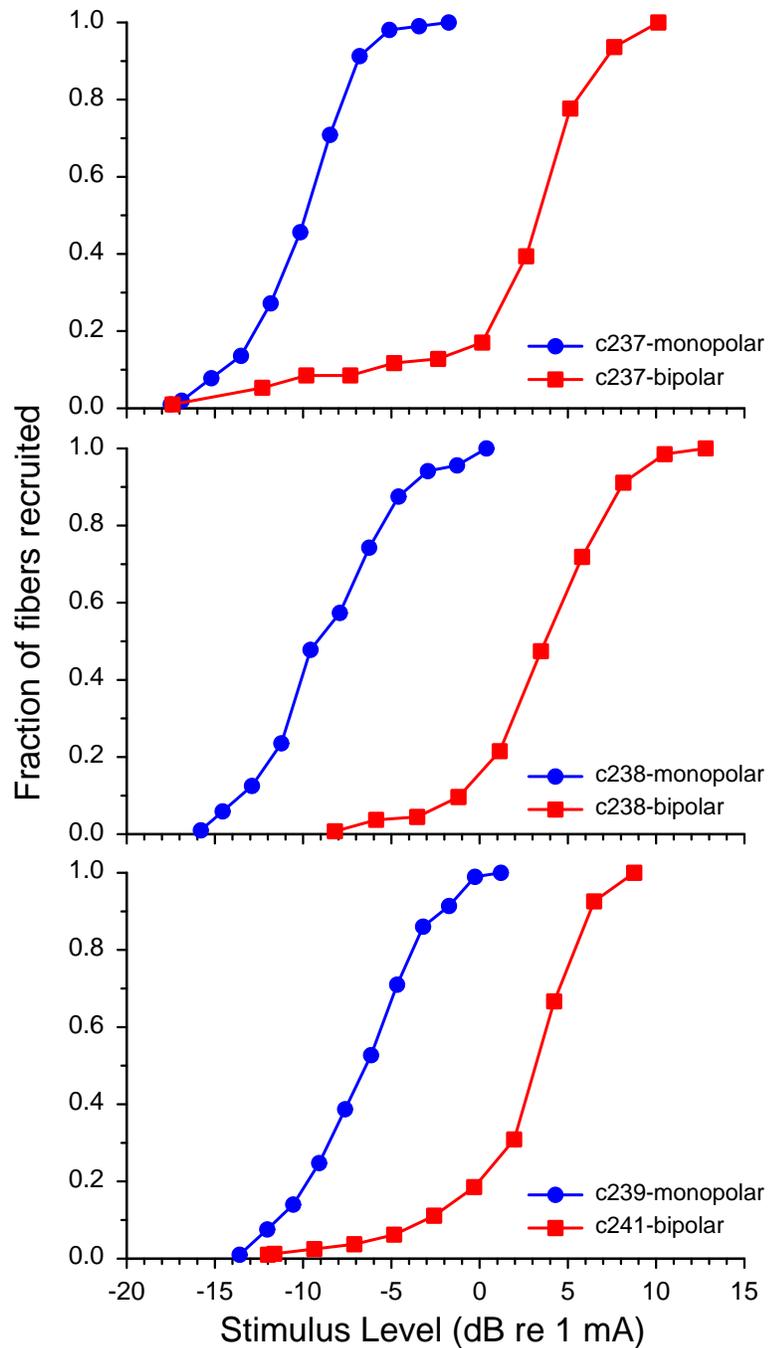


Figure 8: Single-fiber recruitment curves derived from the data shown in Figure 7. Plots were created by first computing threshold histograms and then integrating the histograms across stimulus level. To facilitate across-plot comparisons, data are plotted normalized to the total number of fibers recruited in each case.

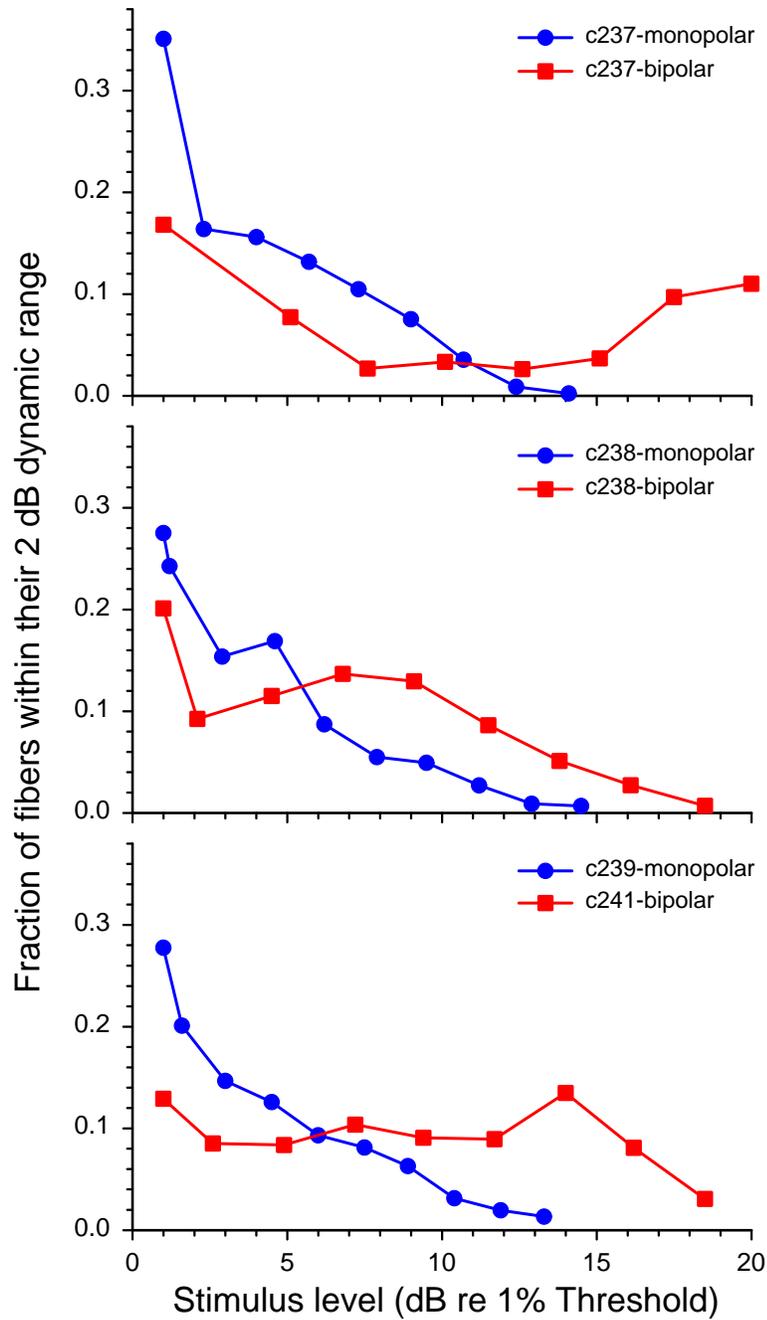


Figure 9: Plots, derived from the data of Figure 8, showing the relative number of actively responding fibers that are not saturated (i.e., FE < 100 %). In each of the three comparisons, monopolar stimulation produced a larger ratio of unsaturated fibers at relatively low stimulus levels.

electrode array) and in the study of van den Honert and Stypulkowski (1987), which used ball electrodes positioned at the base of the scala tympani. This suggests that such differences may be somewhat resistant to changes in the exact placement and construction of the electrodes. We suggest that implant users may also benefit from the neurophysiological differences observed in this study.

4 Plans for the next quarter

In the tenth quarter, we plan to do the following:

- Attend the 2002 Midwinter Meeting of the Association for Research in Otolaryngology. We plan to present several posters on findings directly related to our NPP research contracts.
- Continue experiments investigating the effects of stimulating electrode configuration.
- Continue experiments with the University of Michigan thin-film electrodes. This includes both electrophysiological and histological assessments of their performance in intraneural measurements.
- Apply our Macintosh cluster to the computational modeling of solutions to fiber responses in refractory states.

5 Publications

- Mino H., Rubinstein J.T., White J. (in press) Comparison of algorithms for the simulation of action potentials with stochastic sodium channels. *Annals of Biomedical Engineering*.

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